IOP Conf. Series: Materials Science and Engineering **192** (2017) 012022 doi:10.1088/1757-899X/192/1/012022

Analysis of stochastic dynamics of Higgins model

L Ryashko
Ural Federal University, Lenina, 51, Ekaterinburg, 620000, Russia
E-mail: lev.ryashko@urfu.ru

Abstract. We consider the Higgins model of glycolytic oscillations. An influence of random disturbances on equilibria and cycles of this model is studied. Peculiarities of the dispersion of stochastic trajectories near the deterministic attractors of Higgins model are investigated by the direct numerical simulation and semi-analytical approach based on the stochastic sensitivity functions technique. To describe a spatial arrangement of random states, we use the confidence domains method. The results of comparative analysis of the influence of additive and parametric noise are given.

1. Introduction

At the present time, a significant interest is paid to the study of stochastic dynamics of the biochemical systems. Among a wide variety of biochemical processes, the reaction of glycolysis is one of the most important. In the present paper, we focus on the model introduced by Higgins [1]. This model describes self-sustained oscillations in the yeast glycolytic system. A limit cycle is a standard mathematical model of such oscillations. In the Higgins system, this limit cycle appears as a result of the Andronov-Hopf bifurcation. The deterministic Higgins model is well studied and plays a role of the important tutorial example [2-5].

It is well known that the random noise is an inevitable attribute of any real system. The noise can essentially change the system's dynamics [6-8]. An influence of noise on glycolysis was investigated in [9-11].

In the current paper, we study a stochastic dynamics of glycolysis on the base of Higgins model. In our theoretical analysis, we use the quasipotential method [12] and stochastic sensitivity functions technique [13-15]. This semi-analytical technique was successfully applied to the study of various noise-induced phenomena in nonlinear dynamic systems [16-19].

In Section 2, we study a bifurcation and attractors (equilibria and cycles) of the deterministic Higgins model.

In Section 3, we analyse an influence of random noise on the attractors of Higgins model. Here, we apply the stochastic sensitivity functions technique and the confidence domains method.

An impact of the parametric noise on cycles of the Higgins model is discussed in Section 4.

2. Deterministic model

In this paper, we study the glycolytic oscillations under the random disturbances on the basis of the well known Higgins model [1]

$$\begin{aligned} \dot{x} &= 1 - xy, \\ \dot{y} &= py\left(x - \tfrac{1+q}{q+y}\right). \end{aligned} \tag{1}$$

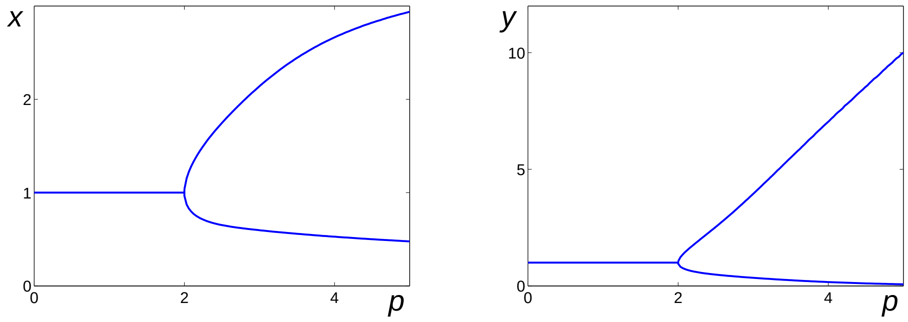

Figure 1. Bifurcation diagrams of the deterministic Higgins model (1) with $q = 1$.

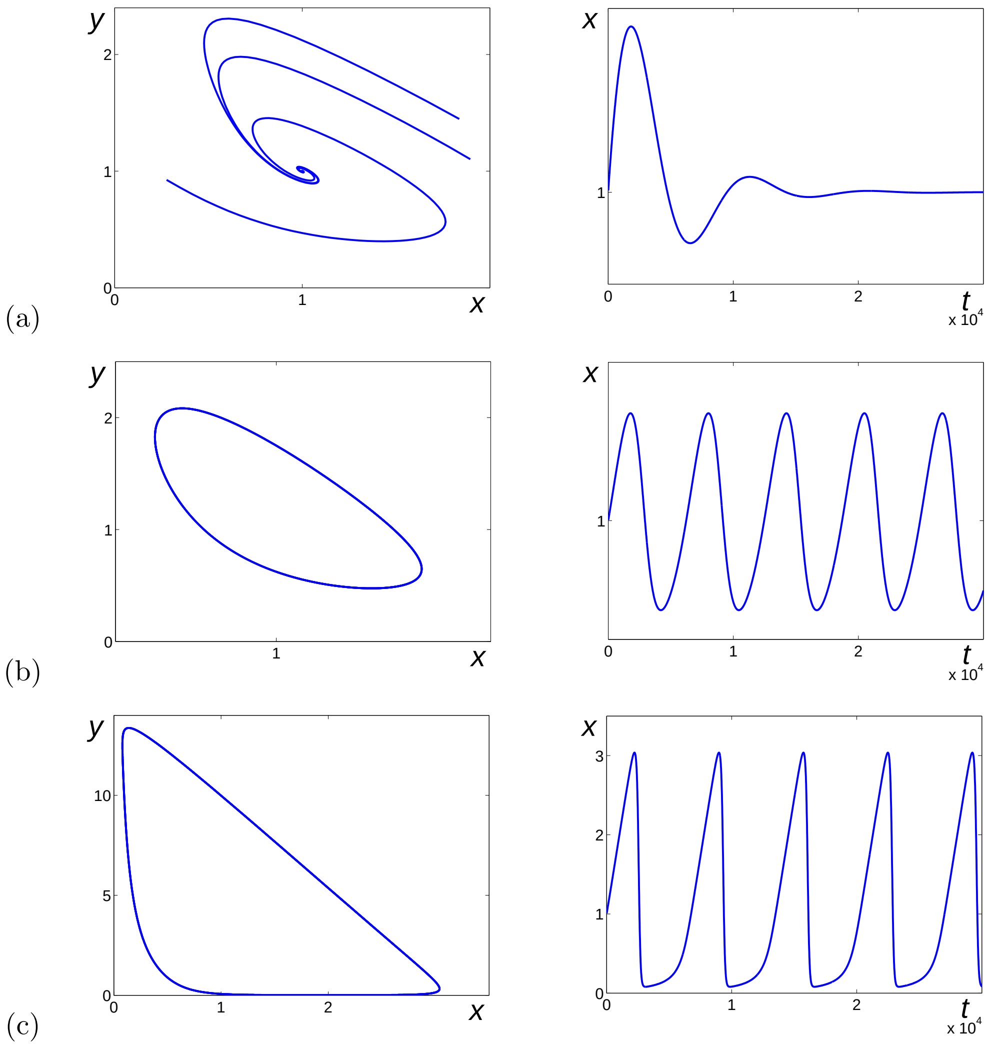

Figure 2. Phase trajectories and time series for the deterministic Higgins model (1) with $q = 1$ and $p = 1$ (a); $p = 2.2$ (b); $p = 5$ (c).

Here, p and q are the positive parameters. The system (1) is a mathematical model of the product-activated and substrate-inhibited reaction.

The parametric line $p = q + 1$ marks the Andronov - Hopf bifurcation. For $0 < p < q + 1$, system (1) has a unique stable equilibrium $\bar{x} = \bar{y} = 1$. For $p > q+1$, this equilibrium is unstable, and system (1) exhibits the stable self-sustained oscillations. In the present paper, we fix $q = 1$ and vary the parameter p.

In Figure 1, a bifurcation diagram of system (1) is presented. Here, the extreme values of x-coordinates of attractors are shown in Fig. 1a, and the extreme values of x-coordinates of attractors are shown in Fig. 1b. As parameter p increases, the amplitude of oscillations increases too, especially for y-coordinate.

For three values of parameter p, the phase portraits and time series are shown in Fig. 2. Note that close to the bifurcation point $p = 2$, the oscillations are quasi-harmonic, and with increasing p, the system exhibits relaxation oscillations.

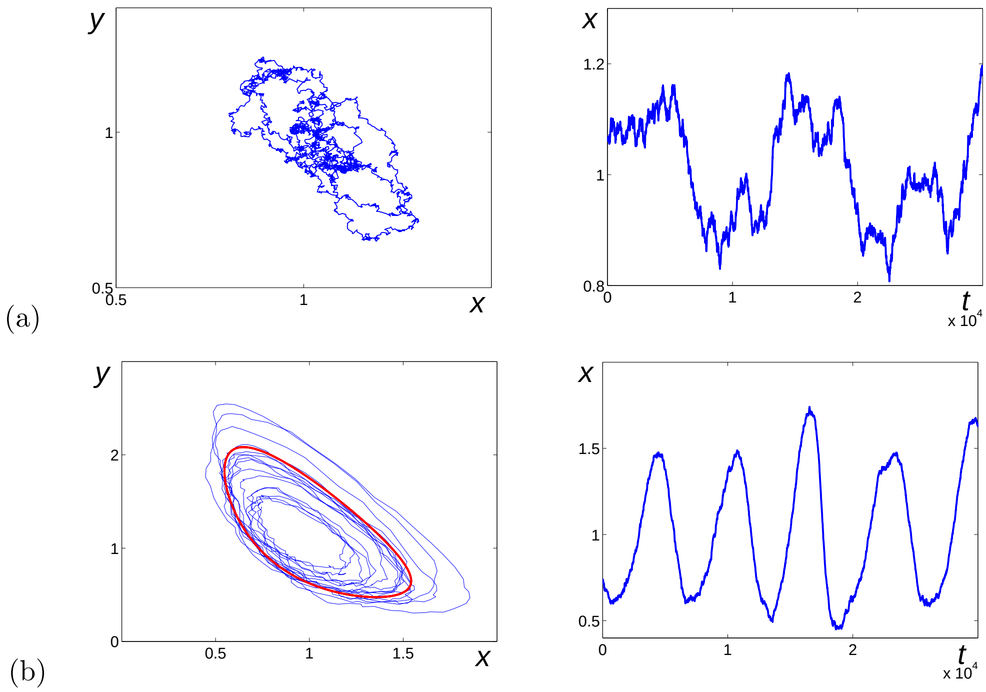

Figure 3. Phase trajectories and time series for the stochastic Higgins model (2) with $q = 1$, $\varepsilon = 0.05$, and $p = 1$ (a); $p = 2.2$ (b). By red shown is the deterministic limit cycle.

3. Stochastic model with additive noise

First, consider an influence of the additive noise modelling by the following stochastic system

$$\begin{aligned} \dot{x} &= 1 - xy + \varepsilon_1 \xi_1(t), \\ \dot{y} &= py\left(x - \frac{1+q}{q+y}\right) + \varepsilon_2 \xi_2(t), \end{aligned} \tag{2}$$

where $\xi_1(t)$ and $\xi_2(t)$ are the uncorrelated standard white Gaussian noises which describe fluctuating external forces, $\varepsilon_{1,2}$ are the additive noise intensities. In what follows, we put $\varepsilon_1 = \varepsilon_2 = \varepsilon$.

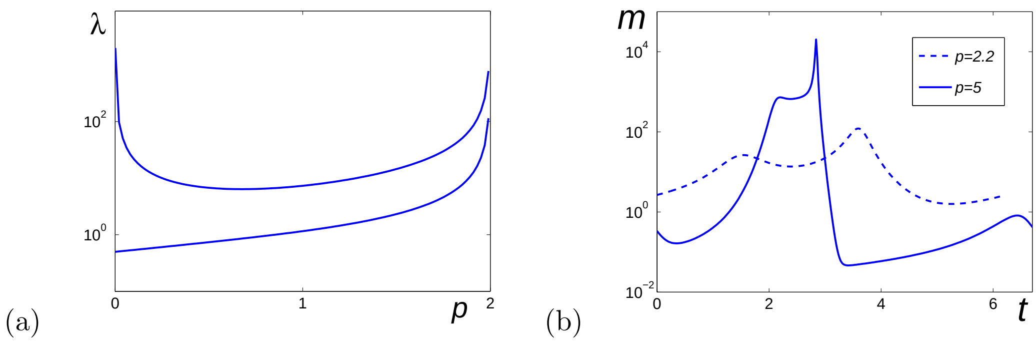

Figure 4. Stochastic sensitivity of equilibria (a) and cycles (b).

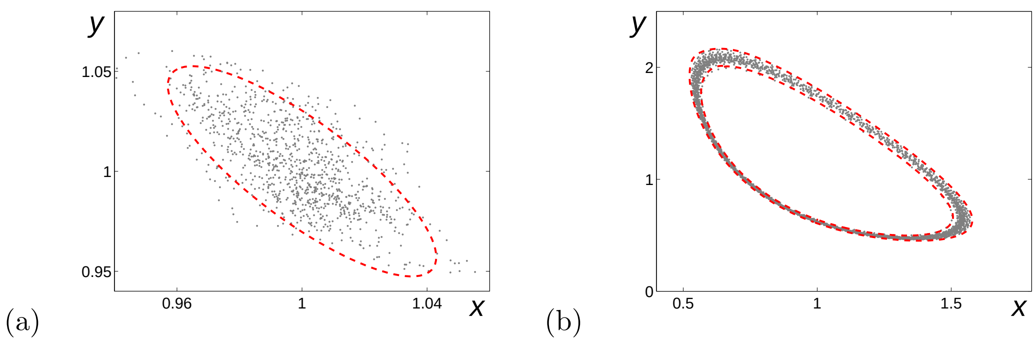

Figure 5. Random states and confidence domains for $\mathcal{P} = 0.99$: (a) ellipse for $p = 1$, $\varepsilon = 0.01$; (b) band for $p = 2.2$, $\varepsilon = 0.003$.

The trajectories of stochastically forced system (2) leave a deterministic attractor (equilibrium or cycle) and form some probabilistic distribution around it. In Fig. 3, the random trajectories and time series for model (2) with $q = 1$ and $\varepsilon = 0.05$ are plotted for the stochastically forced equilibrium with $p = 1$ (see Fig. 3a), and for the stochastically forced cycle with $p = 2.2$ (see Fig. 3b). As one can see, a dispersion of random trajectories near attractors is non-uniform.

To study this dispersion parametrically, we will apply the stochastic sensitivity functions technique.

For the equilibria, this dispersion is defined by the noise intensity and the stochastic sensitivity matrix W [13,14]. Eigenvalues λ_1, λ_2 of this matrix are the simple scalar characteristics of the stochastic sensitivity of equilibrium. In Fig. 4a, functions $\lambda_1(p) > \lambda_2(p)$ are plotted in the zone of stable equilibria for $0 < p < 2$. As can be seen, the largest $\lambda_1(p)$ unlimitedly increases near the left and right borders of this interval. In contrast to $\lambda_1(p)$, the function $\lambda_2(p)$ is monotonous and tends to infinity approaching the Andronov-Hopf bifurcation value $p = 2$. Note that the values of $\lambda_1(p)$ essentially dominate over $\lambda_2(p)$.

For the cycle, the stochastic sensitivity matrix is a T-periodic function $W(t)$. Here, T is the period of solution $(\bar{x}(t), \bar{y}(t))$ which presents a limit cycle. In the two-dimensional case, $W(t) = m(t)v(t)v^{\top}(t)$, where $v(t)$ is a normalized vector orthogonal to the limit cycle. The scalar function $m(t)$ is called the stochastic sensitivity function of cycle [13,14].

Using $m(t)$, we can describe some peculiarities of the dispersion along the cycle in detail. In Fig. 4b, plots of function $m(t)$ for two values of parameter p are shown. Overfalls of its values reflect the non-uniformity of stochastic bundles around cycles. Note for the larger values of p

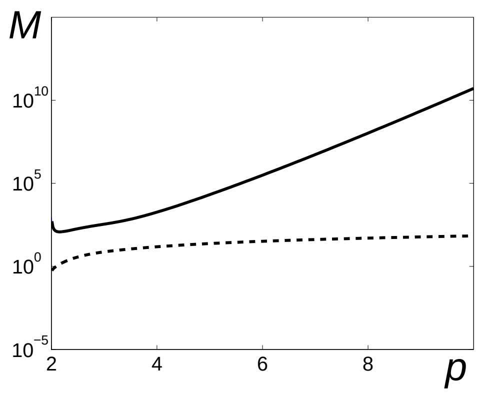

Figure 6. Stochastic sensitivity factors $M(p)$ for the system (2) (solid) and system (3) (dashed).

corresponding to the relaxation oscillations (see the solid line for $p = 5$), the overfall of values of $m(t)$ is more essential.

With the help of stochastic sensitivity function, one can the construct confidence domains around deterministic attractors. The confidence domains are simple and evident geometrical models for the description of arrangement of random states near the deterministic cycles and equilibria. In Fig. 4, along with random states of system (2), a confidence ellipse for $p = 1$, $\varepsilon = 0.01$ around the equilibrium, and confidence band for $p = 2.2$, $\varepsilon = 0.003$ around the limit cycle are shown. As one can see, these confidence domains effectively visualize a spatial arrangement of random states in the phase plane, and well agree with the results of direct numerical simulation.

As a cumulative characteristic of the response of limit cycle on random disturbances, we will use the stochastic sensitivity factor

$$M = \max_{[0,T]} m(t).$$

In Fig. 6, the function $M(p)$ for system (2) is plotted by the solid line.

4. Stochastic model with parametric noise

Consider now the influence of parametric noise on cycles of the Higgins model. Here, we focus on the random disturbances of parameter p. Consider a system

$$\begin{aligned} \dot{x} &= 1 - xy, \\ \dot{y} &= (p + \varepsilon\xi(t))y\left(x - \tfrac{1+q}{q+y}\right), \end{aligned} \tag{3}$$

obtained from system (1) by the replacement $p \to p + \varepsilon\xi(t)$. Here, $\xi(t)$ is a standard white Gaussian noise, ε is an intensity of the parametric noise.

In Fig. 4, a plot of the stochastic sensitivity factor $M(p)$ for system (3) is shown by the dashed line. Here, we can compare the response of limit cycles on the additive (solid line) and parametric (dashed line) noises. Note that the function $M(p)$ for parametric noise is monotonic. The plot of function $M(p)$ for the additive noise is different. Approaching to the bifurcation point $p = 2$, the stochastic sensitivity of the system (2) increases unlimitedly. As parameter p increases, this function decreases, passes a minimum and begins to grow sharply.

5. Conclusion

Attractors of Higgins model forced by random disturbances were studied by the stochastic sensitivity function technique and confidence domains method. An effectiveness of our approach in the analysis of peculiarities of the stochastic dynamics is demonstrated.

6. References

[1] Higgins J 1964 *Proc. Natl. Acad. Sci. U. S.* **51** 989
[2] Bhargava S C 1980 *Bull. Math. Biol.* **42** 829
[3] Gurel D and Gurel O 1983 *Oscillations in Chemical Reactions* (Berlin: Springer-Verlag)
[4] Epstein I R and Pojman J A 1998 *An Introduction to Nonlinear Chemical Dynamics: Oscillations, Waves, Patterns, and Chaos* (New York: Oxford University Press)
[5] Rubin A B 2014 *Fundamentals of Biophysics* (New Jersey: Wiley)
[6] Horsthemke W and Lefever R 1984 *Noise-Induced Transitions* (Berlin: Springer)
[7] Lindner B, Garcia-Ojalvo J, Neiman A and Schimansky-Geier L 2004 *Phys. Rep.* **392** 321
[8] Bashkirtseva I, Ryashko L and Schurz H 2009 *Chaos Solitons Fractals* **39** 72
[9] Garcia-Olivares A, Villarroel M and Marijuán P C 2000 *Biosystems* **56** 121
[10] Xu W, Kong J S and Chen P 2009 *J. Phys. Chem. C* **113** 2393
[11] Schuster P 2016 *Stochasticity in Processes Fundamentals and Applications to Chemistry and Biology* (Berlin: Springer)
[12] Bashkirtseva I and Ryashko L 2011 *Phys. Rev. E* **83** 061109
[13] Bashkirtseva I, Neiman A and Ryashko L 2013 *Phys. Rev. E* **87** 052711
[14] Bashkirtseva I and Ryashko L 2014 *Phys. A* **410** 236
[15] Ryagin MY and Ryashko LB 2004 *Int. J. Bif. Chaos* **14** 3981
[16] Bashkirtseva I and Ryashko L 2009 *Phys. Rev. E* **79** 041106
[17] Bashkirtseva I, Chen G and Ryashko L 2012 *Chaos* **22** 033104
[18] Bashkirtseva I, Ryashko L and Slepukhina E 2014 *Fluct. Noise Lett.* **13** 1450004

Acknowledgments

The work was supported by Russian Science Foundation (N 16-11-10098).